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NOVARTIS

April 8, 2004

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, Maryland 20852

Dear FDA:

Reference to the Federal Register Notice [Docket No. 2004D-0035] and FDA's request for comments on the draft guidance entitled "Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis." The guidance was issued in 1994 (1994 draft guidance).

Herein we provide you with the Novartis comments on the above mentioned guideline for your consideration in developing an updated draft guidance on the same topic.
If you have any questions or comments, please contact me at (862) 778-3665.

Sincerely,

Lynn Mellor

Lynn Mellor
Director
Drug Regulatory Affairs

LM/js

2004D-0035 C5

GENERAL STATEMENT

In developing this recommendation, we considered the following key points

- Recent studies[1,2,3] have shown that an observation period of 1 year is sufficient to demonstrate anti-fracture efficacy that is sustained over a 3 year period with agents that have been shown to produce normal bone quality in preclinical studies.
- Agents that have demonstrated sustained reduction in fracture risk over 3 years and good bone quality clinical studies have likewise demonstrated good bone quality in preclinical models. The failure of etidronate and fluoride to maintain a 3-year fracture benefit was due to poor bone quality. This failure could have been predicted on the basis of preclinical data[4,5,6,7, 8].
- Clinical bone quality and bone safety can be adequately assessed *ex vivo* with bone biopsies using histomorphometry, as well as uCT to provide more detailed information on microstructure. *In vivo* QCT[9,10], pQCT[11,12,13] , and MRI [14,15,16] can be used to provide supplemental information on trabecular and cortical bone structure, in addition to that provided by BMD.
- Ethical concerns over the use of placebo controlled trials have arisen due to the existence of therapies that reduce the risk of fractures. The conduct of placebo controlled studies is becoming increasingly more challenging. thus underscoring the need to develop accepted surrogates for bone strength and fracture outcomes.

1. Treatment of Osteoporosis

A "treatment of osteoporosis" indication can be attained on the basis of a single trial using an 18-24-month fracture endpoint, such as morphometric vertebral fractures and/or all clinical fractures, provided that increases in BMD have been demonstrated in an adequate, well-controlled phase II program, the fracture benefit is supported by biochemical markers of bone turnover, and there is evidence of good bone quality. A claim on hip fracture benefit should be permissible based on a strong positive trend in fracture incidence ($p < 0.2$) provided that reduction in vertebral and non-vertebral fracture risk is demonstrated in the same trial as has been demonstrated with other agents.[17,18]

The patient population to be studied should have no more than a moderate risk of fracture, defined as:

1. T-score >-4.0, as measured by DXA of the femoral neck, and
2. presence of no more than grade 1 vertebral deformities, as determined by semi-quantitative methods.

The 18-month time point is the minimum duration for the observation period. That is, the last patient enrolled is to be followed for 18 months, whereas any patient enrolled prior to the last patient can be observed for up to 24 months or until a clinical fracture event has occurred. Any patient who has had a fracture can be rolled over to active therapy and continued in patient follow-up to allow collection of safety data. Registration should be allowed on the basis of fracture efficacy assessments at 18-24 months, provided there is clinical and preclinical evidence of normal bone quality for new agents within an established class with a known mechanism of action, such as bisphosphonates. For new therapeutics

with a novel mechanism of action, more extensive clinical data on overall safety and bone quality should be required to justify registration based on anti-fracture efficacy at 2 years. This may include a minimum number of patients exposed to the new agent for a period of 3 years, along with assessment of BMD at all relevant sites and the use of emerging imaging technologies to assess bone quality (e.g. CT and MRI) and to predict bone strength (e.g. Finite Element Analysis).

Bone quality should be assessed using bone biopsies, as is the current standard, but can be further supported by newer *in vivo* imaging modalities, such as MRI[19], and more preferably, volumetric spiral CT [20,21] Volumetric spiral CT is preferred since it is a more widely accepted technique and is more readily implemented in large trials.

2. Prevention of Osteoporosis

A "prevention of osteoporosis indication" can be attained in a study population comprised of individuals with low bone mass (BMD T-score = -1 to -2.5), by demonstrating an increase in BMD, as well as maintaining good bone quality. For non-anabolic agents, effective reduction in bone turnover assessed by at least 2 bone biochemical markers, should be demonstrated. Bone quality can be assessed through pre-clinical or clinical biomechanical, or structural (e.g. histomorphometry, MRI, uCT) tests. A "treatment" claim need not precede a "prevention" claim provided that preservation of bone quality is demonstrated. Again, we believe preclinical models are predictive of bone quality in humans.[22]

PRECLINICAL STUDIES

Preclinical studies should aim at characterizing the effect of a compound on bone mass, cancellous and cortical bone architecture and material properties in skeletally mature, at least 6 month old rats, and in adult nonhuman primates.

- Bone mineral content and density should be measured by DXA in lumbar vertebral bodies and by DXA/pQCT in the appendicular skeleton (femur or tibia).
- Cortical bone architecture should be determined by pQCT of the femur or tibia.
- Trabecular bone architecture should be determined, if possible, by microCT[23] or static histomorphometry.
- Bone remodeling is an essential contributor to bone health, especially for adaptive processes, tissue renewal and repair of microdamage. At present, there is no suitable alternative to replace the fluorochrome based dynamic histomorphometric assessments. These measurements provide crucial information on the 'mode of action' of novel compounds and at least in rodents are more reliable than plasma or urinary parameters of bone formation and/or resorption. They should remain an essential part of the guidance.
- In studies involving bone anabolic agents, changes in the rate of Haversian remodeling should be assessed in non human primates in view of the finding, that agents like PTH and GH are potent activators of cortical remodeling. [24, 25]
- At present, there is no easy, reliable alternative to mechanical testing of vertebral bodies in compression or long bones in 3-point or 4-point bending. This is a reliable

way to get information on changes in material properties (stiffness) in addition to overall bone strength.

1. Study duration: non-human primates

Based on experience with bisphosphonates, SERMs and PTH, two time points should be used for the assessment of parameters described above:

- **Transient effects** should be assessed at 3 to 6 months by analysis of plasma/serum biomarkers of bone formation, as well as plasma and/or urinary biomarkers of resorption[26,27,28], changes in vertebral and tibia (femur) BMD by DXA and of cortical and trabecular BMD by pQCT [29,30]
- **Steady state** conditions should be assessed at 18 months and should include all the above in addition to the mechanical endpoints.[31] In addition, dynamic histomorphometric parameters should be used as end point at 18 months to assess bone turnover[32] combined with a histopathological assessments to spot abnormal 'woven' bone formation or mineralization defects.

2. Study duration: rats

Based on experience with bisphosphonates, SERMs and PTH, two time points should be used for the assessment of parameters described above:

- **Transient effects** Parameters that should be assessed during the 'transient' phase should include analysis of plasma/serum biomarkers of bone formation, as well as plasma and/or urinary biomarkers of bone resorption[33], changes in vertebral and tibia (or femur) BMD by DXA[34]and of cortical and trabecular BMD by pQCT in the tibia. In addition, dynamic histomorphometric parameters should be used as end point at 1-2 months to assess bone turnover combined with a histopathological assessments to spot abnormal 'woven' bone formation or mineralization defects.[35,36]
- **Steady state** conditions should be assessed at 6 months of treatment and should include all the above plus the mechanical endpoints such as vertebral compression tests and 3- or 4-point bending of the femur mid-shaft. [37,38]

CLINICAL STUDIES

1. Trial design and statistical considerations for a placebo-control study in post-menopausal osteoporosis

With the changing ethical climate in the field of osteoporosis within the US, designing placebo-controlled trials that evaluate fracture endpoint(s) in osteoporosis has become increasingly difficult. However, with proper definitions of the population being studied and statistical decision rules being applied that allow for some flexibility, placebo-controlled studies can continue to be conducted for the time being. In the near future, it will become practically impossible to conduct placebo-controlled studies, underscoring the urgent need to define acceptable surrogates for fracture outcomes to avoid prohibitively large active comparator fracture endpoint studies (see below). Given this, the following suggestions and recommendations are made for placebo-controlled trials:

a. To study a population that has baseline vertebral deformities for reduction in morphometric vertebral fracture incidence, the participating population must consent that they either cannot or do not choose to take existing therapies for osteoporosis. It is

recognized that many IRBs/ERCs may not approve the conduct of such trials even with these stipulations, and that obstacles to the practical implementation of placebo studies in osteoporosis will only increase over time.

b. If reduction in morphometric vertebral fractures is the primary endpoint, this can be evaluated either by showing a statistically significant reduction in the proportion of subjects with at least one new morphometric fracture, or by showing a statistically significant reduction in morphometric vertebral fractures by evaluating changes at the individual vertebra level, keeping patient as the primary unit of analysis.

- If the intention is to show a reduction in the overall morphometric vertebral fracture incidence, then the analysis must show significance at an overall 0.05 level of significance. The preferred method is either logistic regression or a stratified non-parametric analysis method, which will allow for adjustments to be made for the number of baseline fractures
- If x-rays are taken at multiple time points, it is permissible to define O'Brien-Fleming boundaries and/or an α-spending function. An interim analysis may be conducted at an earlier time point to demonstrate statistical significance as long as this earlier look allows the overall significance level to be maintained at the 0.05 level. This is done under the assumption that the requirements for patient exposure and long-term safety data will be satisfied.
- It should be permissible to evaluate fracture reduction using generalized estimating equation (GEE) methods that examine changes at the individual vertebral level over time. With this methodology, additional information is obtained from multiple fractures, but at a discount accounting for the correlation structure, and keeping the patient as the primary unit of analysis.

c. If reduction in morphometric vertebral fractures and all clinical and/or non-vertebral fractures are the desired efficacy co-endpoints, then this can be implemented by applying a closed testing procedure which will allow the preservation of a pre-specified overall statistical significance level.

- All clinical fracture endpoints can be evaluated using event-driven survival analysis methods, stratifying for the presence of any background osteoporosis therapies received by participating patients if such therapies are allowed per study protocol.
- If, as part of the closed testing procedure, a statistically significant reduction in morphometric vertebral fractures has been demonstrated, then, since anti-fracture efficacy has been established, it should be permissible that only a trend towards statistical significance be demonstrated ($p < 0.1$ for all clinical fractures, $p < 0.2$ for hip fractures).
- If interim analyses are conducted, the hurdle for demonstrating an effect on clinical/hip fractures should be higher as specified by the O'Brien-Fleming boundaries and/or an α-spending function, as such an interim analysis of the clinical fracture endpoints maintains the overall pre-specified level of significance for the test.
- It should be permissible to utilize multiple event methods (e.g. Anderson-Gill) that allow for the multivariate evaluation of clinical fractures across all locations. Flexibility should be allowed as necessary if the baseline variables that affect the incidence of the different type of clinical fracture differ from site-to-site.

- How missing x-ray data will be handled in the statistical analysis should be clearly specified in the protocol and/or the statistical analysis plan. The handling of two situations should be clearly described: (1) imputation for patients who provide no x-ray data to the analysis either at baseline and/or during the post-randomization period, and (2) imputation or adjustments for patients who prematurely discontinue from the study and do not provide x-ray measurements at all time points.

2. Trial design and statistical considerations for a non-inferiority study in post-menopausal osteoporosis

In the near future it may become extremely difficult to conduct placebo-controlled studies in osteoporosis. With clear definition of conditions for study participation and the risk involved, it is believed that non-inferiority studies can be used in populations previously studied in placebo-controlled studies limited to higher risk populations (i.e. those populations where patients have an existing vertebral fracture or a recent hip fracture). Under such a paradigm, the main areas in need of clarification are a) how to define non-inferiority bounds to conduct such studies, and b) what the primary endpoint should be.. The considerations for these studies are the following:

a. The active comparator used in such a trial must have established efficacy in those fracture endpoints that are planned to be evaluated.

b. While it may be possible to conduct active comparator studies for vertebral fracture endpoints, alternative endpoints are necessary for assessment of benefit for clinical and hip fracture events due to the prohibitively large sample sizes that would be required.

c. If the incidence of new morphometric vertebral fracture is the primary efficacy endpoint being evaluated, the chosen non-inferiority margin, based on the data from a placebo-controlled fracture study conducted with the active control, must allow for the preservation of at least 2/3 of the treatment effect observed in the placebo-controlled study conducted with the active control.

   - The preservation of at least 2/3 of the treatment effect defined above will ensure a claim of superiority over (hypothetical) placebo if conducted against any of the osteoporosis therapies with demonstrated anti-fracture efficacy. Thus, this margin will be sufficient to protect against a creep toward placebo-like efficacy.
   - The decision on efficacy would be based on whether or not the upper bound of the 95% confidence interval of the difference in the proportion of subjects with new morphometric vertebral fractures (Test drug minus active control) exceeded the above defined margin.
   - Interim stopping rules should still be permissible in these designs for demonstrating superiority and/or futility; however, early stopping for non-inferiority would not be permissible.

d. If clinical and/or hip fracture are/is desired to be studied in the same clinical study, alternative endpoints to assess bone mass and bone quality, as predictors of bone strength, could be used to demonstrate non-inferiority to avoid the excessively large numbers of patients that would be required for a fracture endpoint. These parameters may include BMD, QCT, and MRI (with or without finite element modeling for bone strength).

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e. Rules for the handling of missing x-ray data for placebo-control studies also apply to the active-control design.

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